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ORIGINAL ARTICLE

A novel method for the synthesis of nicotinonitrile and diazepin derivatives under microwave irradiation

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Abstract Ethyl 2-aryl-3-dimethylamino-acrylates **2a**,**b** were prepared *via* the reaction of ethyl arylacetate with *N*,*N*-dimethylformamidedimethylacetal (DMFDMA) under microwave irradiation. Reaction of **2a**,**b** with malononitrile afforded the corresponding substituted malononitrile derivatives **4a**,**b**, which underwent intramolecular cyclization in boiling acetic acid, containing a catalytic amount of ammonium acetate, to give unexpected products 2-amino-6-hydroxy-5-(4-nitrophenyl)nicotinonitrile derivatives **6**. Whereas **2a** reacted with *o*-phenylenediamines under microwave irradiation to yield diazepin-4-ol derivative **9**. On the other hand, reacting the enaminoesters **2a**,**b** with urea and thiourea, as nitrogen nucleophiles, by heating under microwave yielded the pyrimidinone derivatives **12a**–**d**.

1. Introduction

Functionally substituted enamines are versatile reagents and their chemistry has recently received considerable interest (Storck et al., 1954; Wittig and Blumenthal, 1927; Hiroi et al., 1986). In our previous work, we have explored the synthetic potentialities of enaminones and enaminonitriles utilizing both conventional and microwave (MW) heating (Almazroa et al., 2004; Al-Sheikh et al., 2004a,b, 2007, 2008; Ghozlan et al., 2004). Microwave heating has been employed for the rapid synthesis of a wide variety of organic molecules (Lerestif et al., 1997; Gedye et al., 1986; Loupy et al., 1998; Caddick, 1995) wherein chemical reactions are accelerated because of the selective absorption of MW energy by polar molecules. Non-polar molecules are inert to the MW dielectric loss (Desai et al., 2007; Tan et al., 2006; Varma, 2001). The applications of microwave irradiation with the use of catalysts or mineral-supported reagents, under solvent-free conditions, provide unique chemical processes with special attributes such as enhanced reaction rates, higher yields, greater selectivity and the ease of manipulation. This prompted us to describe herein, a new synthetic approach for the synthesis of novel derivatives of diazepin and pyrimidinone, utilizing microwave irradiation as the energy source.

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2. Experimental

2.1. General

All melting points were measured on a Gallenkamp electrothermal melting point apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Pye Unicam SP 3-300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d_6) at 300 and 400 MHz on a Varian Gemini NMR spectrometer using tetramethyl silane (TMS) as an internal reference and the results are expressed as δ values. Mass spectra were performed on a Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microwave irradiation was carried out using the commercial microwave oven (SGO 1000 W). Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University, Egypt.

2.2. General procedure for the preparation of ethyl 3-(dimethylamino)-2-arylacrylates **2a**,**b**

To a solution of ethyl phenyl acetate (**1a**) or ethyl 4-nitrophenyl acetate (**1b**) (0.01 mol) in DMF (1 mL), DMFDMA (0.012 mol) was added. Then, the mixture was irradiated in a microwave oven for 2 min. After cooling to room temperature, ethanol (5 mL) was added and the mixture was left overnight. The precipitated crystals were collected by filtration and washed with ethanol to give **2b** and their data are in agreement with our previous work (Salaheldin and Al-Sheikh, 2010).

2.3. General procedure for the preparation of compounds (**4a**,**b**)

A mixture of **2a**,**b** (10 mmol), malononitrile (10 mmol) and drops of acetic acid was irradiated in a microwave oven for 5 min. The resulting solid product was filtered off and recrystallized from the proper solvent.

2.4. 4,4-Dicyano-2-phenyl-but-2-enoic acid ethyl ester (**4a**)

Compound **4a** was obtained as brown crystals (93%), mp 276 °C; ^{1}H NMR (DMSO-d_6) δ: 1.29 (t, 3H, CH_3), 3.8 (d, 1H, J = 7.5 Hz, H-4), 4.20 (q, 2H, CH_2), 7.2–7.6 (m, 5H, Ar-H), 7.8 (d, 1H, J = 7.5 Hz, H-3). ^{13}C NMR (DMSO-d_6) δ: 160.5 (CO), 142.2 (C-2), 140 (C-1′), 126.4 (C-3′, C-5′),126.3 (C-3), 124.9 (C-2′, C-6′), 120.5 (C-4′), 116 (CN), 53.9 (OCH_2), 14.8 (C-4), 14.2 (CH_3). MS (EI, 70 eV): m/z = 240 (M^+). Anal. Calcd. for $C_{14}H_{12}N_2O_2$ (240.26): C, 69.99; H, 5.03; N, 11.66. Found: C, 70.01; H, 4.99; N, 11.73.

2.5. 4,4-Dicyano-2-(4-nitrophenyl)-but-2-enoic acid ethyl ester (**4b**)

Compound **4b** was obtained as brown crystals (96%), mp 95 °C; ^{1}H NMR (DMSO-d_6) δ: 1.18 (t, 3H, CH_3), 3.87 (d, H, J = 7.2 Hz, H-4), 4.12 (q, 2H, CH_2), 7.5 (d, 2H, J = 8.08 Hz, Ar-H), 8.0 (d, H, J = 7.2 Hz, H-3), 8.2 (d, 2H, J = 8.08 Hz, Ar-H). ^{13}C NMR (DMSO-d_6) δ: 170.2 (CO), 147 (C-4′), 140 (C-1′), 135 (C-2), 130.8 (C-3′, C-5′), 128 (C-3), 123.3 (C-2′, C-6′), 119 (CN), 60.5 (OCH_2), 14.32 (C-4), 14.01 (CH_3). MS (EI, 70 eV): m/z = 284 (M^+-1). Anal. Calcd. for $C_{14}H_{11}N_3O_4$ (285.25): C, 58.95; H, 3.89; N, 14.73. Found: C, 59.01; H, 3.98; N, 14.59.

2.6. General procedure for the preparation of 2-amino-6-hydroxy-5-(4-nitrophenyl)nicotinonitrile (**6**)

To a solution of **4b** (10 mmol) in acetic acid (4 mL), ammonium acetate (10 mmol) was added. Then, the reaction mixture was refluxed for 3 h. After cooling to room temperature, the resulting solid product was collected by filtration and recrystallized from acetic acid to give **6** as brown crystals (95%), mp 283 °C; IR (KBr): v = 3404 (OH), 3381 (NH_2), 2210 (CN). ^{1}H NMR (DMSO-d_6) δ: 7.7 (brs, 2H, NH_2), 7.95 (d, 2H, J = 8.0 Hz, Ar-H), 8.06 (s, 1H, H-4), 8.29 (d, 2H, J = 8.0 Hz, Ar-H), 10.15 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 171.44 (C-6), 163.50 (C-2), 146.71 (C-4′), 144.16 (C-1'), 142.67 (C-4), 130.81 (C-5), 129.71 (C-2′, C-6′), 123.92 (C-3′, C-5′), 116.22 (CN), 79.05 (C-3). MS (EI, 70ev): m/z = 255 (M^+-1). Anal. Calcd. for $C_{12}H_8N_4O_3$ (256.22): C, 56.25; H, 3.15; N, 21.87. Found: C, 56.33; H, 3.09; N, 21.75.

2.7. General procedure for the preparation of 3-phenyl-1H-benzo[b][1,4]diazepin-4-ol (**9**)

A mixture of **2a** (10 mmol), *o*-phenylenediamine (**7**) (10 mmol) and drops of acetic acid was irradiated in a microwave oven for 2 min. The resulting solid product was filtered off and recrystallized from ethanol to give compound **9** as gold yellow crystals; yield (89%), mp 159–162 °C; IR (KBr): v = 3363 (OH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 7.29 (d, 1H, H-6); 7.31–7.32 (m, 1H, H-8); 7.33–7.34 (m, 1H, H-7); 7.46 (d, 1H, NH); 7.47–7.48 (m, 1H, H-4́); 7.49–7.51 (m, 2H, H-3́, 5́); 7.52 (d, 1H, J = 8 Hz, H-2); 7.82 (d, 1H, J = 8 Hz, H-9); 8.30 (d, 2H, J = 8 Hz, H-2',6́); 12.56 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ = 115.07 (C-7), 123.36 (C-8), 127. 83 (C-4́), 128.74 (C-9), 129.18 (C-2́, 6́), 130.17 (C-3́,5́), 130.29 (C-2), 132.00 (C-3,6), 132.04 (C-1a), 135.61 (C-1́), 154.12 (C-5a), 154.57 (C-4). MS (EI, 70 eV): m/z = 235 (M^+). Anal. Calcd. for $C_{15}H_{12}N_2O$ (236.27): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.03; H, 4.98; N, 12.00.

2.8. General procedure for the preparation of compounds **12a**–**d**

A mixture of **2a**,**b** (10 mmol), urea (**10a**) or thiourea (**10b**) (10 mmol) and drops of acetic acid was irradiated in a microwave oven for 3 min. The resulting solid product was filtered off and recrystallized from proper solvent.

2.9. 5-Phenyl-1H-pyrimidin-2,4-dione (**12a**)

Compound **12a** was obtained as yellow crystals (95%), mp 242 °C; IR (KBr): v = 3225 (NH), 1682 (CO). ^{1}H NMR (DMSO-d_6) δ: 6.2 (brs, H, NH), 7.12–7.40 (m, 5H, Ar-H), 8.2 (s, H, pyrimidine H-6), 10.1 (d, H, NH). ^{13}C NMR (DMSO-d_6) δ: 167.52 (CO), 154.39 (CO), 136.64 (C-1′), 133.80 (C-6), 130.10 (C-3′,5′), 128.15 (C-2′, 6′), 126.78 (C-4′), 110.55 (C-5). MS (EI, 70 eV): m/z = 188 (M^+). Anal. Calcd. for $C_{10}H_8N_2O_2$ (188.18): C, 63.82; H, 4.28; N, 14.89. Found: C, 63.69; H, 4.01; N, 14.79.

2.10. 5-(4-Nitrophenyl)-1H-pyrimidin-2,4-dione (**12b**)

Compound **12b** was obtained as yellow crystals (95%), mp 214 °C; ^{1}H NMR (DMSO-d_6) δ: 6.5 (brs, H, NH), 7.5 (d, 2H, J = 8.08 Hz, Ar-H), 8.2 (d, 2H, J = 8.08 Hz, Ar-H),

8.58 (s, H, pyrimidine H-6), 10.16 (d, H, NH). ^{13}C NMR (DMSO-d_6) δ: 164.14 (CO), 152 (CO), 147 (C-4′), 140 (C-1′), 132 (C-6), 127.21 (C-3′, C-5′), 123.52 (C-2′, C-6′), 112.5 (C-5). MS (EI, 70 eV): m/z = 236 ($M^+ + 3$). Anal. Calcd. for $C_{10}H_7N_3O_4$ (233.18): C, 51.51; H, 3.03; N, 18.02. Found: C, 51.42; H, 2.96; N, 18.11.

2.11. 5-Phenyl-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (**12c**)

Compound **12c** was obtained as yellow crystals (95%), mp 299 °C; ^{1}H NMR (DMSO-d_6) δ: 6.12 (s, 1H, pyrimidine H-6), 7.3–7.6 (m, 5H, Ar-H), 7.9 (brs, H, NH), 13.2 (s, H, NH). ^{13}C NMR (DMSO-d_6) δ: 175.2 (CS), 160.7 (CO), 147 (C-6), 132.9 (C-1′), 128.6 (C-3′, C-5′), 128.3 (C-2′,C-6′), 128.1 (C-4′), 117.2 (C-5). MS (EI, 70 eV): m/z = 204 (M^+). Anal. Calcd. for $C_{10}H_8N_2OS$ (204.25): C, 58.80; H, 3.95; N, 13.72. Found: C, 59.0; H, 4.01; N, 13.95.

2.12. 5-(4-Nitrophenyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (**12d**)

Compound **12d** was obtained as yellow crystals (95%), mp 177 °C; ^{1}H NMR (DMSO-d_6) δ: 7.2 (s, 1H, pyrimidine H-6), 7.57 (d, 2H, J = 8.08 Hz, Ar-H), 8.20 (d, 2H, J = 8.08 Hz, Ar-H), 8.1 (brs, H, NH), 13.3 (s, H, NH). ^{13}C NMR (DMSO-d_6) δ: 180.2 (CS), 170.8 (CO), 147 (C-6), 146 (C-4′), 140 (C-1′), 131.4 (C-3′, C-5′), 125.9 (C-2′, C-6′), 114.3 (C-5). MS (EI, 70 eV): m/z = 249 (M^+). Anal. Calcd. for $C_{10}H_7N_3O_3S$ (249.25): C, 48.19; H, 2.83; N, 16.86. Found: C, 48.20; H, 2.75; N, 16.79.

3. Results and discussion

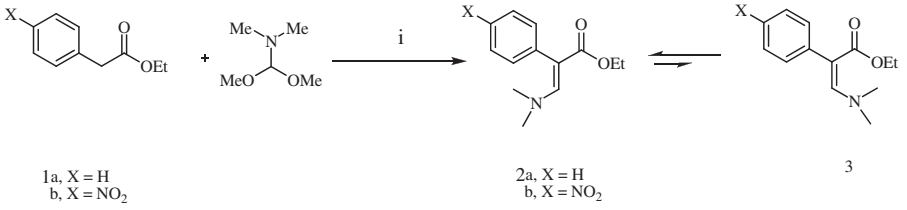
In conjunction with this work, we report herein the synthesis of enaminoesters **2a**,**b** and its reactivity toward some selected nitrogen and carbon nucleophiles utilizing microwave irradiation as the energy source. Thus, the reaction of ethyl phenyl acetate **1a** or ethyl *p*-nitro-phenyl acetate **1b** with *N*,*N*-dimethylformamidedimethylacetal (DMFDMA) by heating with microwave gave the enaminoesters **2a**,**b**, in good yields. Although compounds **2a**,**b** may also adopt *cis* form **3**, structure **2** was confirmed based on NOE difference experiment that revealed special proximity of dimethylamino function and aryl protons (Scheme 1). Although structure **3** looks less sterically crowded, structure **2** satisfies better the stereo electronic factors (Kirby, 1996).

When compounds **2a**,**b** were reacted with malononitrile by heating the neat reagents with microwave, an nucleophilic substitution took place at C-3 in **2** that led directly to the new 2-aryl-4,4-dicyano-but-2-enoic acid ethyl ester **4a**,**b**, in excellent yields. Compounds **4b** underwent intramolecular cyclization in refluxing acetic acid, containing a catalytic amount of ammonium acetate, to furnish the interesting 2-amino-6-hydroxy-5-(4-nitrophenyl)nicotinonitrile **6** *via* the intermediate **5** (Scheme 2).

The structure of **6** was confirmed as the reaction product from its IR, ^{1}H NMR and correct elemental analysis as well as mass spectrum. Thus, the IR spectrum of **6** revealed the absence of the ester carbonyl group and the presence of the absorption bands at ν = 3404, 3381 and 2210 cm^{-1} due to the OH, NH_2 and cyano, respectively. The ^{1}H NMR gave strong evidence for the formation of **6** which displayed the disappearance of the ethoxy group signal presented in the spectrum of **4b** and the presence of two singlet signals at δ = 8.06 and 7.7 ppm attributable to CH at C-4 and NH_2, respectively. Furthermore, its mass spectrum shows the molecular ion m/z 255 ($M^+ - 1$) confirming its presumed structure. Analytical data are in accordance with the proposed structure for compound **6**.

We investigated that the reaction of **2a** with *o*-phenylenediamine (**7**) under MW might afford the corresponding 2-phenylacrylamide derivative **8** or diazepine derivative **9**. Interestingly, however, an unexpected new compound 3-phenyl-1*H*-benzo[b][1,4]diazepin-4-ol **9** was obtained (Scheme 3). The identity of compound **9** was supported by correct elemental analysis and spectral data. Thus, IR spectrum of **9** revealed the presence of a broad absorption band at 3363 cm^{-1} corresponding to OH stretching and the absence of C=O absorption. The ^{1}H NMR spectrum displayed the presence of a singlet signal at 12.56 ppm (D_2O exchanged), assignable to the diazepin OH, besides signals due to aromatic protons in their expected positions. Additionally, its structure was fully confirmed by ^{13}C NMR which was compatible with the suggested structure. Furthermore, its mass spectrum has the molecular ion m/z = 235 (84%), confirming its presumed structure. Analytical data are in accordance with the proposed structure for compound **9**. The formation of compound **9** was assumed to proceed *via* the initial condensation of the amino group of *o*-phenylenediamine with the ester group of the enamino ester **2a** to give the intermediate **8**, which then undergoes intramolecular cyclocondensation to give the isolated final product **9** (Scheme 3).

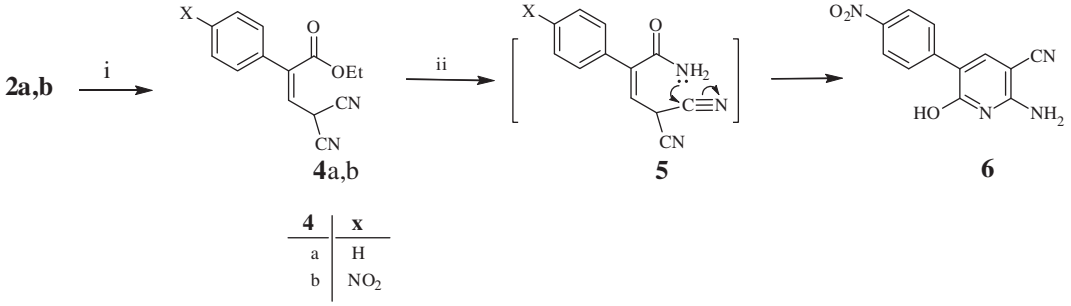
However, the reaction of **2a**,**b** with urea (**10a**) or thiourea (**10b**) under microwave irradiation for 3 min at 400 W afforded 5-arylpyrimidin-2,4(1*H*, 3*H*)-diones **12a**,**b** and 5-aryl-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-ones **12c**,**d**, respectively. Formation of **12** can be accounted for by the condensation of **2** with urea or thiourea, with the loss of one molecule of dimethylamine, to give the ring-opened intermediate **11**. Subsequent



(i) ethyl phenylacetate, DMF, MW, 2 min (**2a**);

(ii) ethyl *p*-nitro-phenylacetate, DMF, MW, 2 min (**2b**);

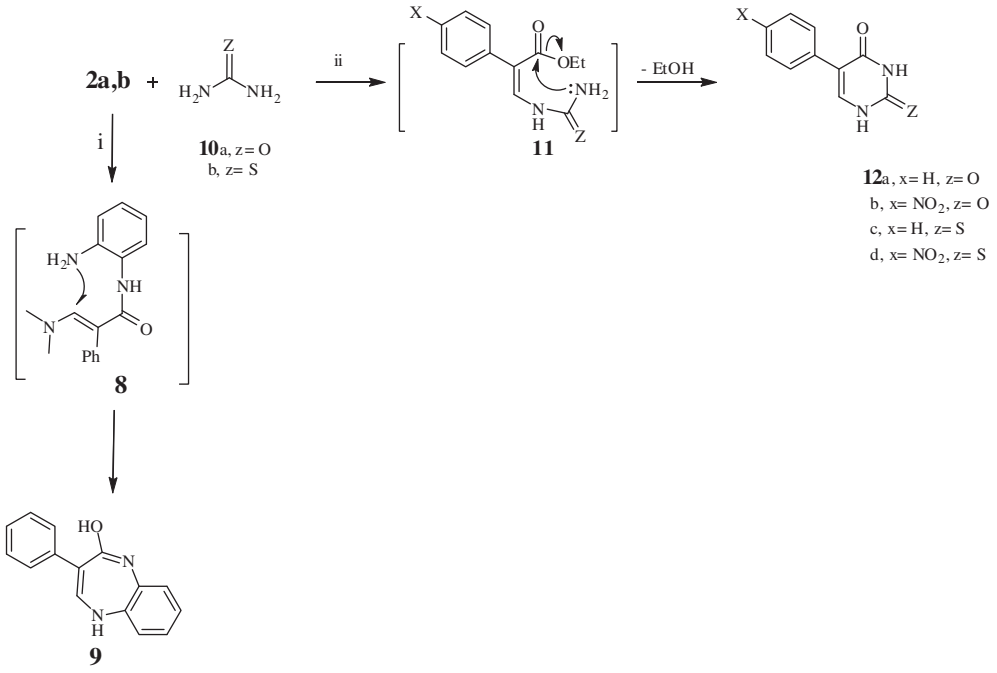
Scheme 1



(i) Enaminoester, $CH_2(CN)_2$, drop AcOH, MW, 5 min **(4a,b)**

(ii) 4,4-Dicyano-2-(4-nitrophenyl)-but-2-enoic acid ethyl ester 4b, AcOH/ $AcONH_4$, reflux, 3h **(6)**

Scheme 2



(i) Enaminoester 2a, o-Phenylenediamine, drop AcOH, MW, 2 min **(9)**

(ii) Enaminoester, urea, MW, 3 min **(12a,b)**;

(iii) Enaminoester, thiourea, MW, 3 min **(12c,d)**;

Scheme 3

intramolecular cyclocondensation leads to the final product **12** (Scheme 3).

The structures of compounds **12a–d** were substantiated on the basis of spectral and analytical data. Particularly, the ^{1}H NMR spectra which revealed the absence of ethoxy and dimethylamino group signals presented in the spectrum of **2** and the presence of two singlets at $\delta \approx 6.2$ and 10.1 ppm, for **12a**,**b**, and at $\delta \approx 8$ and 13.3 ppm, for **12c**,**d**, assignable to two pyrimidine NH. Moreover, ^{13}C NMR spectroscopy indicated the presence of carbonyl and thiocarbonyl carbons at $\delta \approx 161.9$ and 179.7 ppm, respectively, in addition to pyrimidine and aryl carbons as expected for structure **12** (see Section 2).

4. Conclusion

We have developed a green methodology for the synthesis of new derivatives of nicotinonitrile, diazepine and pyrimidinone. The present protocol offers several advantages such as (a) clean and simple reaction procedure, (b) isolation of the products without purification methods like column chromatogra-

phy and (c) avoiding volatile and toxic organic solvents. Furthermore, this neat reaction under MWs gave excellent yield of products with lesser reaction time.

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